I U C L I D

Data Set

Existing Chemical	:	ID: 1984-58-3
CAS No.	:	1984-58-3
EINECS Name	:	2,5-dichloroanisole
EC No.	:	217-852-6
Molecular Formula	:	C7H6Cl2O

Producer related part

Company	:	Arcadis
Creation date	:	04.10.2007

Substance related part

Company	:	Arcadis
Creation date	:	04.10.2007
Status	:	
Memo	:	
Printing date	:	22.05.2008
Revision date	:	
Date of last update	:	22.05.2008
Number of pages	:	23
Chapter (profile)	:	Chapter: 1.2, 2.1, 2.2, 2.4, 2.5, 2.6.1, 3.1.1, 3.1.2, 3.1.3, 3.3.1, 3.3.2, 3.5, 4.1, 4.2, 4.3, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.4, 5.5, 5.6, 5.8.1, 5.8.2
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.2 SYNONYMS AND TRADENAMES

2.1 MELTING POINT

Value	:	= 19.9 °C
Sublimation	:	
Method	:	OECD Guide-line 102 "Melting Point/Melting Range"
Year	:	2004
GLP	:	yes
Test substance	:	other TS
Method	:	The melting temperature was measured according to OECD 102, using differential scanning colorimetry. A PC controlled DSC instrument (Model DSC 204 of Netzsch), calibrated with a certified set of standards, was used. Measurement was carried out with Al2O3 as a crystallization aid. A preliminary test was run between -120 and 400 degrees C. Decomposition was not observed. In the definitive test, two heating cycles were run.
Remark	:	EPIWIN v3.20 estimates the melting temperature to be 20.65 deg C.
Result	:	The melting temperature was determined to be 19.9 degrees C (mean of two heating cycles).
Test substance	:	2,5-dichloroanisole, CAS No. 1984-58-3, batch identification: release number 13418. The test substance is a liquid at room temperature.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

15.10.2007 (1)

2.2 BOILING POINT

Value	:	= 231.3 °C at 1016.1 hPa
Decomposition	:	
Method	:	OECD Guide-line 103 "Boiling Point/boiling Range"
Year	:	2004
GLP	:	yes
Test substance	:	other TS
Method	:	Determined by dynamic method according to Annex Commission Directive 92/69/EEC, A.2.
Remark	:	EPIWIN v3.20 estimates the boiling temperature to be 215.7 deg C.
Result	:	The normal boiling temperature was obtained by interpolation to be 231.0 degrees C at a vapour pressure of 1013.25.
Test substance	:	2,5-dichloroanisole, CAS No. 1984-58-3, batch identification: release number 13418. The test substance is a liquid at room temperature.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

15.10.2007 (1)

2.4 VAPOUR PRESSURE

Value	:	= .07 hPa at 25 °C
Decomposition	:	
Method	:	Directive 92/69/EEC, A.4
Year	:	2004
GLP	:	yes
Test substance	:	other TS
Method	:	The vapour pressure was determined by dynamic method according to Annex Commission Directive 92/69/EEC, A.4. Vapour pressure measurements were made over a range of 53.95 deg C - 231.30 degrees

C. The vapour pressures were extrapolated from the regression equation.

Remark : EPIWIN v3.20 estimates the vapour pressure to be 0.22 hPa (Mackay Method).

Result : The vapour pressures calculated at different temperatures are presented below:

Temp (deg C)	VP (hPa)
20	0.04
25	0.07
50	0.51

Test substance : 2,5-dichloroanisole, CAS No. 1984-58-3, batch identification: release number 13418. The test substance is a liquid at room temperature.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

09.10.2007 (1)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = 3.5 at 24 °C
pH value : = 7.4
Method : Directive 92/69/EEC, A.8
Year : 2004
GLP : yes
Test substance : other TS

Method : The experiment was performed in accordance with Annex Commission Directive 92/69/EEC, A.8, shake flask method.

Two standard solutions of the test substance were made in 50 mL of water-saturated n-octanol: 93.30 mg / 50 mL and 88.62 mg / 50 mL. Three samples were prepared from each stock solution: 1:1, 1:2, and 2:1 v/v water:octanol saturated with water at ambient temperature (= 24 +/- 1 deg C). The n-octanol phases were diluted with water / acetonitrile (45:55 v/v) following separation. The water phases were applied undiluted. Samples were analyzed for test substance content using HPLC and subsequent UV detection. For calibration, the test substance was dissolved in acetonitrile and diluted with water/acetonitrile (45:55 v/v).

Remark : EPWIN v3.20 estimates the log Pow to be 3.36.

Result : Three measurements were made for each of the two standard solutions. The resultant values for log Pow were: 3.47, 3.50, 3.45, 3.43, 3.70 and 3.62. The mean was 3.53, with a standard deviation of 0.11.

Test substance : 2,5-dichloroanisole, CAS No. 1984-58-3, batch identification: release number 13418. The test substance is a liquid at room temperature.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

15.10.2007 (1)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 84 - 90 mg/l at 20 °C
pH value : = 7.1 - 7.4
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C

Description	:	
Stable	:	
Deg. product	:	
Method	:	Directive 92/69/EEC, A.6
Year	:	2004
GLP	:	yes
Test substance	:	other TS
Method	:	The experiment was performed in accordance with Annex Commission Directive 92/69/EEC, A.6, flask method. 22.14 - 30.36 mg of the TS and 50 mL of water were shaken at 30 degrees C for 24, 48, 72, and 96 hours. The mixtures were then conditioned for 24 hours at 20 degrees C and then filtered and analyzed using HPLC with UV detection. For calibration, the test substance was dissolved and diluted with water/acetonitrile.
Remark	:	EPIWIN v3.20 estimates the water solubility to be 76 mg/L at 25 deg C.
Result	:	The mean (n = 4) water solubility was 87 +/- 3 mg/L at 20 degrees C (+/- 1 degree C).
Test condition	:	The pH of the solutions was maintained at neutral (7.1-7.4).
Test substance	:	2,5-dichloroanisole, CAS No. 1984-58-3, batch identification: release number 13418. The test substance is a liquid at room temperature.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

09.10.2007 (1)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .0000000000052463 cm³/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	
Year	:	2001
GLP	:	
Test substance	:	

Method : Estimation using AOP program v1.92 in EPIWIN v3.20. Experimentally determined values for melting point, boiling point and water solubility were used as physical property inputs.

Result :

AOP Program (v1.92) Results:
==========
SMILES : O(c(c(ccc1CL)CL)c1)C
CHEM : Benzene, 1,4-dichloro-2-methoxy-
MOL FOR: C7 H6 CL2 O1
MOL WT : 177.03
---------- SUMMARY (AOP v1.92): HYDROXYL RADICALS ----------
Hydrogen Abstraction = 0.8296 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 0.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings = 4.4167 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 5.2463 E-12 cm3/molecule-sec
HALF-LIFE = 2.039 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 24.465 Hrs
---------- SUMMARY (AOP v1.91): OZONE REACTION ----------

****** NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database: NO Structure Matches
Fraction sorbed to airborne particulates (phi): 1.86E-005 (Junge,Mackay)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Test substance	:	2,5-Dichloroanisole CAS 1984-58-3
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

15.10.2007 (2)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 1 year at 25 °C

t1/2 pH7	:	> 1 year at 25 °C
t1/2 pH9	:	> 1 year at 25 °C
Deg. product	:	
Method	:	
Year	:	2001
GLP	:	no
Test substance	:	
Method	:	Estimated on chemical principles based on absence of groups susceptible to hydrolysis
Remark	:	The estimation program in EPIWIN has no capability to estimate hydrolysis rates for this compound
Result	:	This material has no groups that are susceptible to hydrolysis in the pH 4 to 9 range; therefore, it is considered stable to hydrolysis in surface and groundwater. It is estimated to have a hydrolysis half-life of greater than one year between pH 4 and pH 9.
Source	:	Toxicology and Regulatory Affairs Flemington NJ
Test substance	:	2,5-Dichloroanisole CAS 1984-58-3
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

26.12.2001 (3)

3.1.3 STABILITY IN SOIL

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: calculated
Year	:	
Method	:	Fugacity was determined using the EQC Level III model as found in EPIWIN v3.20. Experimentally determined values for melting point, boiling point, and water solubility were used as physical property inputs. Equal emissions to air, soil and water were assumed.
Result	:	Level III Fugacity Model (Full-Output):

==========

Chem Name : Benzene, 1,4-dichloro-2-methoxy-
Molecular Wt: 177.03
Henry's LC : 0.00315 atm-m3/mole (Henrywin program)
Vapor Press : 0.0742 mm Hg (Mpbpwin program)
Log Kow : 3.36 (Kowwin program)
Soil Koc : 939 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.41	48.9	1000
Water	17.8	900	1000
Soil	74.9	1.8e+03	1000
Sediment	0.927	8.1e+03	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)

Air	1.23e-10	1.26e+03	893	42.2	29.8
Water	2.2e-08	191	248	6.36	8.27
Soil	4.51e-08	402	0	13.4	0
Sediment	2.44e-08	1.11	0.258	0.0368	0.00861

Persistence Time: 465 hr
Reaction Time: 750 hr
Advection Time: 1.22e+003 hr
Percent Reacted: 62
Percent Advected: 38

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 48.94
Water: 900
Soil: 1800
Sediment: 8100
Biowin estimate: 2.337 (weeks-months)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Test substance : 2,5-Dichloroanisole CAS 1984-58-3
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
15.10.2007 (2)

3.3.2 DISTRIBUTION

3.5 BIODEGRADATION

Type : aerobic
Inoculum : other: Municipal activated sludge, non-adapted
Concentration : 50 mg/l related to Test substance
related to
Contact time : 28 day(s)
Degradation : < 10 (±) % after 28 day(s)
Result : under test conditions no biodegradation observed
Kinetic of testsubst. : 0 day(s) = 0 %
5 day(s) < 0 %
13 day(s) < 0 %
19 day(s) < 0 %
28 day(s) < 0 %
Control substance : Aniline
Kinetic : 14 day(s) = 74 %
28 day(s) = 80 %
Deg. product :
Method : OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
Year : 2004
GLP : yes
Test substance : other TS

Method : This test follows the OECD 301 F guideline for biodegradability determination through manometric respirometry.

ThOD was calculated assuming that C is mineralized to CO2, H to H2O, Na to Na2O, and the halogens to hydrogen halide. Nitrogen is elminated as ammonia and not oxidized to nitrate or nitrite; sulfur is assumed to be oxidized to a state of +VI. The resulting value was 1356 mgThOD/g test substance.

The inoculum used was municipal activated sludge from laboratory wastewater treatment plants fed with municpal sewage. The reference substance was aniline, which has a ThOD of 2393 mgThOD/g.

The exposure time was 28 days. Biodegradation was calculated as %BOD/ThOD after 28 days.

The following controls were also run: blanks, reference substance biodegradation, inhibition of the inoculum, and abiotic elimination. Seven replicates of the test substance were run. An eighth replicate, TS 8, was run so that pH determinations could be made.

Remark : OECD 301 F states under the test conditions that the pH of the experimental vessels must be maintained at pH 7.4 (+/-0.2) throughout the experiment. The results show a clear starting pH value for the aniline reference control and the blanks outside of this range; however, this was corrected by the addition of 1 drop of 1M H2SO4. This was also added to each run containing the test substance to ensure an adequate pH. pH readings were not taken during the course of the experiment. Final pH values were taken for all experimental runs and all but the reference substance and the inhibition of the inoculum control were within the accepted range.

The concentration of the test substance was reported as "about 50 mg/L." OECD 301F requires the test substance concentration to be 100 mg/L.

Test substance : The test substance is 2,5-dichloroanisole (CAS 1984-58-3), batch #13418. Purity was determined by GC analysis as 99.3%. The test substance was stored at room temperature throughout the course of the experiment.

Conclusion : The mean value of the seven test substance replicates was -10% BOD/ThOD after 28 days. Thus, the test substance falls into the <10% category and is classified as "poorly biodegradable."

Reliability : (1) valid without restriction
Substantially complies with guideline.

22.05.2008 (4)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= 1 measured/nominal
LC0	:	= 1 measured/nominal
LC50	:	= 2.4 measured/nominal
LC100	:	= 4.7 measured/nominal
Limit test	:	no
Analytical monitoring	:	yes
Method	:	EPA OPPTS 850.1075
Year	:	2005
GLP	:	yes
Test substance	:	other TS

Method : A 96 hour semistatic test was conducted according to: EPA-Para.72-1; EPA-SEP No.540/9-85-006; OPPTS 850.1075; 92/69/EEC, Annex V, C1; and OECD 203. The rainbow trout were hatched at the testing facility and were approximately 2 months of age at the time of exposure. The mean wet weight and body length were 0.59 g and 4.2 cm respectively. The health of the animals was observed at the beginning of the experiment; no signs of sickness, injuries, or anbnormalities were observed.

The trout were acclimatized to the experimental test conditions for 14 days prior to the experiment with diet withdrawl during the last 24 hours. The test water was non-chlorinated charcoal-filtered tap water mixed with deionized water and had a harndess of approx. 100 mg/L CaCO3, a conductivity of approx. 250uS/cm (at 25 degrees C), a pH generally between 7.5-8.5, and a temperature of approx. 14-15 degrees C. During the 14 day acclimation period the dissolved oxygen content of the water was maintained above 80% of air saturation.

Dilutions of the test substance were prepared daily and separately for each vessel. The test substance was diluted in 50 L of test water to reach the following nominal concentrations (mg/L): 0, 1.0, 2.2, 5.0, 10.0, and 22.0.

The animals were assigned to a vessel according to a randomization plan prepared by the testing laboratory. The test animals were observed within 1 hour of the start of exposure and at hours 4, 24, 48, 72, and 96 for survival and toxic signs (changes in appearance, swimming behavior, comparison of behavior to the control group). Dead fish were removed from the test vessels. Temperature, oxygen content, and the pH were measured following the beginning of the exposure period, shortly before the end of each of the 4 test intervals, and hourly measurements of water temperature were made in one of the aquariums.

Test concentrations were confirmed by analysis of samples taken at 2 intervals: from freshly prepared test water and before test water renewal for the second and last interval. Samples were taken from the middle of the test vessels using a glass pipette.

The LC50 was calculated using probit analysis and 95% confidence intervals reported where possible.

Finney, D.J., Probit Analysis; Cambr. Univ. Press, 3rd ed., 1971 (certain aspects of this method have been modified).

Result : All measured concentrations were within 80-120% of nominal during the

exposure period, with mean measured concentrations 88-103% of nominal. Control animals and animals exposed to 1 mgTS/L were asymptomatic throughout the exposure period. Animals exposed to 2.2 mg/L were asymptomatic at the 1 hour interval; however, most showed apathy by the end of the exposure period and there was one mortality each at the 48 and 72 hour interaval and 2 mortalities at the 96 hour interval. Animals exposed to 5 mg/L showed apathy at 1 hour and all but 2 were dead at the 4 hour interval and all were dead at the 24 hour interval. Animals exposed to 10 mg/L and 22 mg/L were all dead at the 1 hour interval.

The effect concentrations were calculated based on the mean measured concentrations of the test substance. The LC50 at 24, 48, 72 and 96 hours was 3.2, 2.5, 2.5 and 2.4 mg/L, respectively. The NOEC at all exposure intervals was 1.0 mg/L.

Test condition : The exposure was conducted in a semistatic system with a full water renewal every 24 hours. The test vessels were glasss aquaria with a stainless steel frame (60cm x 35cm wide x 40cm high). The water depth in vessels was about 27cm. 10 animals were placed in each vessel during the experiment with 50L of test water. The loading of each vessel was 0.1 gFish/L water. Two test vessels were maintained at each experimental concentration. The light intensity was approx. 36-191 Lux and the test temperature was 14-15 deg C. The dissolved oxygen content of the test water was maintained above 60% of air saturation throughout the duration of the exposure. No aeration or feeding was conducted during the 96 hour exposure period.

Test substance : The test substance is 2,5-dichloroanisole (CAS 1984-58-3), Batch No. 13418. A certificate of analysis confirms that the purity of the substance upon testing was 99.3%. The test substance, a homogenous, colorless, liquid, was stored at room temperature.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

15.10.2007 (5)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	semistatic
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50 based on nominal concentrations	:	= 9.44
EC50 based on mean measured concentrations	:	= 5.89
Analytical monitoring	:	yes
Method	:	OECD Guide-line 202
Year	:	2005
GLP	:	yes
Test substance	:	other TS

Method : A semistatic test was conducted in which the test solutions were renewed after 24 hours. Daphnids aged 2-24 hours old, from in-house cultures, were used to start the test. Animals were not fed during exposure. Animals were cultured and tested in synthetic fresh water (M4 medium prepared per ISO 10706), with a hardness of 2.43 mmol/L, conductivity 602 uS/cm and pH 8.1. The M4 medium was aerated for approx. 24 hours to attain oxygen saturation.

The test substance was stirred in M4 medium for about 20 hours at 20 +/- 2

degrees C. Undissolved test substance was removed by centrifugation. The eluate appeared clear and colorless and was used to prepare six nominal test concentrations: 1.56, 3.13, 6.25, 12.5, 25 and 50 mg/L. The control was medium with no test substance added. Analytical determination of the test concentrations was performed at 0 hours, 24 hours (old and new test solutions), and 48 hours.

Four replicate test vessels (20 mL test tubes with flat glass bottoms, containing 10 mL of test solution) were used per test treatment. Five daphnids were impartially added to each test vessel (loading 0.5 animals/mL), for a total of 20 organisms per test treatment. Immobilization was observed at 0, 24, and 48 hours. Dissolved oxygen and pH were measured at 0, 24 and 48 hours in old and new test solutions. Temperature was measured continuously in a separate test vessel. The EC values were calculated using the probit method.

Result : Measured concentrations of test substance ranged from 64.9-85.9% of nominal at the beginning of the test but declined to 36.7-42.7% after 24 hours. Similar results were obtained on the fresh solutions prepared to renew the test. The mean measured concentrations ranged from 59.3%-66.7% of nominal and were: 0.925, 1.93, 3.90, 7.78, 16.0 and 33.4 mg/L.

Dissolved oxygen during the test ranged from 8.4-8.8 mg/L, pH from 8.0-8.1, and temperature from 19.7-20.1 degrees C.

By 48 hours, complete immobilization of daphnids occurred at the two highest test concentrations, with significant immobilization at 12.5 mg/L and essentially no immobilization at the lower test concentrations. No immobilization and no capture of daphnids in the surface film occurred in the controls. The resultant 48-h EC0, EC50 and EC100 values based upon the nominal concentrations were 6.25, 9.44 and 25 mg/L, respectively. The 48-h EC0, EC50 and EC100 values based upon the mean measured concentrations were 3.90, 5.89 and 16.0 mg/L, respectively.

Test condition : The test was conducted at a temperature of 18-22 degrees C (max. temperature difference 2 degrees C). Illumination was provided by warm white lights (intensity about 1-8 uE/m2s at a wavelength of 400-750 nm) on a photoperiod of 16 h day: 8 h night.

Test substance : The test substance is 2,5-dichloroanisole (CAS 1984-58-3), batch #13418. Purity was determined by GC analysis as 99.3%. The test substance was stored at room temperature throughout the course of the experiment.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

17.10.2007 (6)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
Limit test	:	no
Analytical monitoring	:	yes
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	2005
GLP	:	yes
Test substance	:	other TS

Method : The study was conducted according to OECD 201 and EPA OPPTS 850.5400. The test organism was Desmodesmus subspicatus (formerly known as Scenedesmus subspicatus). The nominal inoculation density used in the experiment was 1E4 cells/mL. Three replicates were run for

both the experimental vessels and the control.

The test medium was prepared according to OECD Guideline 201 (OECD medium).

The stock solutions were prepared separately for each concentration and were stirred for approx. 20 hours at 20 +/- 2 degrees C and then centriuged. The two highest test concentrations could not be centrifuged due to a technical defect of the centrifuge. For the centrifuged solutions, the supernatant was decanted and used for testing. Nominal test concentrations were 0, 3.13, 6.25, 12.5, 25 and 50 mg/L. The test substance was not completely soluble in OECD medium.

Test concentrations were run in triplicate along with a triplicate control.

The test parameter was in vivo chlorophyll-a fluorescence (435nm), which was measured in each replicate at 0, 24, 48, and 72 hour intervals by a Fluorometer EOS Fl2. Cell counting was performed after 72 hours in a counting chamber (Neubauer improved) in replicate No.2 of the inoculated control and the data used to construct a calibration curve between fluorescence and cell counts.

The temperature was continuously monitored throughout the 72 hour exposure. The pH was measured at time zero and at 72 hours in an additional uninoculated replicate and after 72 hours in the inoculated replicate No.1 of each concentration.

Result : Measured concentrations of the test substance decreased dramatically during the experiment. Analytical determinations of the test substance in the 50, 25, and 12.5 mg/L solutions showed that concentrations had decreased to 2.4-3.2% of the nominal concentrations. In the 3.13 and 6.25 mg/L solutions no test substance could be detected. The authors hypothesize that this may be due to sensitivity of the test substance to the light used in the experiment.

Population growth was completely inhibited at the highest test concentration, partially inhibited at the 25 mg/L test concentration, and unaffected at the three loweset test concentrations. Test results were calculated based upon both biomass (the integral of growth over test duration) and growth rate.

The results based on the mean analytically determined concentrations, mg/L, are:

EbC50 8.1
NOEbC 4.817

ErC50 10.1
NOErC 4.817

The results based on the nominal concentrations, in mg/L, are:

EbC50 19.2
NOEbC 12.5

ErC50 23.0
NOErC 12.5

The following test validity criteria were met: Cell multiplication in the control after 72 hours was 25-fold. Variation in pH within 72 hours in the control was not more than 2 units.

Test condition : The test vessels (250 mL Erlenmeyer flasks) were illuminated in artificial light, type white universal (ORSAM L 25), under continuous illumination.

The intensity was about 60-120 uE/(m2*s) at a wavelength of 400-700 nm.

Test substance : 2,5-dichlorophenol, Batch#13418, purity 99.3% as stated on certificate of analysis. The test substance is a homogenous, colorless, liquid.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

17.10.2007 (7)

5.1.1 ACUTE ORAL TOXICITY

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	males: 35 days, females: 44 days
Frequency of treatm.	:	One time per day at the same time in the morning.
Post exposure period	:	
Doses	:	0 mg/kg/d, 50 mg/kg/d, 150 mg/kg/d, 450 mg/kg/d
Control group	:	yes, concurrent vehicle
NOAEL	:	= 150 mg/kg bw
Method	:	OECD combined study TG422
Year	:	2006
GLP	:	yes
Test substance	:	other TS

Method :

Male and female Wistar rats aged 11-12 weeks were used in the study. All animals were free of disease and females non-pregnant at the beginning of the study. The males and females were raised from separate litters to prevent possible sibling mating.

Three experimental test groups, plus a control, were run with 10 animals of each sex in each group. Dosage levels were 50 mg/kg/d (the expected no adverse effect level dose), 150 mg/kg/d, and 450 mg/kg/d. The control group was treated identically to the experimental animals except for dosage of the test substance. The test substance was administered dissolved in 0.5% carboxymethylcellulose solution in double distilled water and Tween 80. Controls received 0.5% carboxymethlycellulose solution in double distilled water and Tween 80. All animals received 10 mL/kg/d of solution.

TEST SUBSTANCE PREPARATION

The test substance was weighed in a calibrated beaker, topped up with 0.5% Carboxycellulose solution in double distilled water and a few drops of Tween 80 and mixed with a magnetic stirrer. These emulsions were prepared at the beginning of the study and every 7-8 days afterward, based on the results of a stability study which indicated the test emulsions were stable at room temperature for up to 10 days. Analytical monitoring of the test substance preparations was performed at the beginning of the study.

EXPERIMENTAL PROCEDURE AND TIME SCHEDULE

Following acclimation of about 6 days, 80 animals were selected for use. The mean weight of the 40 male animals was 301.4 g (282.3-321.9) and for the 40 female animals 206.8 g (189.4-220.5). Animals were randomly assigned to test groups in a manner that resulted in similar body mass values in each experimental group.

Dosing was conducted once daily via gavage at approximately the same time each day. This was carried out until 1 day prior to sacrifice. After experimental day 13, males and females from the same dose group were placed in mating cages at a 1:1 ratio.

On study day 31 motor activity measurements and a functional observational battery were carried out on the first 5 males (by randomly assigned ID numbers) in each group. On study day 35, blood from all F0 males was sampled under Isofluorane anesthesia followed by necropsy. A functional observational battery and motor activity measurement were carried out on females on experimental day 43. Blood samples from 5 F0 females was taken under Isofluorane anesthesia on day 44 followed by necropsy.

Checks were made twice daily for moribund or dead animals (once daily on weekends and holidays). Moribund animals were necropsied. Detailed clinical observations were made in all animals once before test substance administration and at weekly intervals thereafter. Food consumption of the F0 animals was determined during premating and in dams during gestation and lactation periods. In general, body weights of F0 animals were determined once a week.

Methods relevant to the reproduction and developmental portion of this study are described in Section 5.8.1 and 5.8.2.

Result **:** FOOD CONSUMPTION: Food consumption of males in all substance-treated groups was similar to that of controls; however it was not measured during premating days 7-14. Food consumption of females in the highest dose group was significantly decreased during premating week 1 and during lactation days 0-4, and this effect was considered to be substance-related.

BODY WEIGHT / BODY WEIGHT CHANGES: Body weight for both males and females was comparable to the control group during the premating period and after weaning. The body weight changes for the high dose females were statistically significantly decreased during gestation days 0-7 and lactation days 0-4.

CLINICAL OBSERVATIONS: Temporary salivation after dosing was observed but was not assessed as an adverse or toxic effect. During study weeks 2 and 3, two out of 10 high dose males had urine smeared fur, which may be an indication of an impaired general condition. No other abnormalities were found.

FUNCTIONAL OBSERVATIONAL BATTERY: No test substance-related findings.

MOTOR ACTIVITY MEASUREMENT: No test substance-related findings.

CLINICAL PATHOLOGY: No treatment-related effects in hematology and enzymes. Slight changes observed in various blood chemistry parameters in high dose males and a marginal increase in inorganic phosphate in high dose females. These mild effects were considered to be not toxicologicaly significant and thus assessed as not being treatment-related.

PATHOLOGY: Substance-related findings occurred in the liver, thyroid glands and kidneys. The absolute and relative kidney weights of males in

the mid and top dose groups were statistically significantly increased in a dose-related manner. There was a slight increase in the incidence and severity of chronic nephropathy in the top dose group.

GROSS LESIONS: A single lesion was detected, but was unrleated to the test substance.

Test condition : Animals were housed individually in stainless steel wire mesh cages (floor area about 800 cm2), with the following exceptions: for the overnight mating, the females were put into the cages of the males; from day 18 p.c. until sacrifice, the pregnant females were housed in Makrolon cages with their litters. Cages were kept in air conditioned rooms at a temperature of 20-24 degrees C and relative humidity 30-70%. The photoperiod was 12 hours light: 12 hours dark. The food was ground Kilba maintenance diet mouse/rat, and tap water was provided for drinking water. Food and water were available ad libitum except during the fasting period and measurement of motor activity.

Test substance : 2,5-dichloroanisole, Batch# 13418, CAS# 1985-58-3. Purity 99.3% as stated on certificate of analysis.

Conclusion : The NOAEL for general, systemic toxicity of the test substance is 150 mg/kg/d for the F0 parental rats of both sexes. This is based upon impairments of food consumption and body weight data for the high dose females and a higher incidence and severity of chronic progressive nephropathy in the high dose males.

Reliability : (1) valid without restriction
26.12.2007 (8)

5.5 GENETIC TOXICITY 'IN VITRO'

5.6 GENETIC TOXICITY 'IN VIVO'

5.8.1 TOXICITY TO FERTILITY

Type : other: combined repeated dose with reproductive/developmental toxicity screening
Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : gavage
Exposure period : males: 35 days; females: 44 days
Frequency of treatm. : once per day at the same time in the morning
Premating exposure period
Male : 13 days
Female : 13 days
Duration of test : males: 35 days; females: 44 days
No. of generation studies :
Doses : 0 mg/kg/d, 50 mg/kg/d, 150 mg/kg/d, 450 mg/kg/d
Control group : yes, concurrent vehicle
NOAEL parental : = 450 mg/kg bw
NOAEL F1 offspring : = 450 mg/kg bw
Result : NOAEL for reproductive performance and fertility is the highest dose tested, 450 mg/kg/d.
Method : OECD Guide-line 422
Year : 2006
GLP : yes
Test substance : other TS

Method : Male and female Wistar rats aged 11-12 weeks were used in the study. All animals were free of disease and females non-pregnant at the beginning of the study. The males and females were raised from separate litters to prevent possible sibling mating.

Three experimental test groups, plus a control, were run with 10 animals of each sex in each group. Dosage levels were 50 mg/kg/d (the expected no adverse effect level dose), 150 mg/kg/d, and 450 mg/kg/d. The control group was treated identically to the experimental animals except for dosage of the test substance. The test substance was administered dissolved in 0.5% carboxymethylcellulose solution in double distilled water and Tween 80. Controls received 0.5% carboxymethlycellulose solution in double distilled water and Tween 80. All animals received 10 mL/kg/d of solution.

TEST SUBSTANCE PREPARATION

The test substance was weighed in a calibrated beaker, topped up with 0.5% Carboxycellulose solution in double distilled water and a few drops of Tween 80 and mixed with a magnetic stirrer. These emulsions were prepared at the beginning of the study and every 7-8 days afterward, based on the results of a stability study which indicated the test emulsions were stable at room temperature for up to 10 days. Analytical monitoring of the test substance preparations was performed at the beginning of the study.

EXPERIMENTAL PROCEDURE AND TIME SCHEDULE

Following acclimation of about 6 days, 80 animals were selected for use. The mean weight of the 40 male animals was 301.4 g (282.3-321.9) and for the 40 female animals 206.8 g (189.4-220.5). Animals were randomly assigned to test groups in a manner that resulted in similar body mass values in each experimental group.

Dosing was conducted once daily via gavage at approximately the same time each day. This was carried out until 1 day prior to sacrifice. After experimental day 13, males and females from the same dose group were placed in mating cages at a 1:1 ratio.

Checks were made twice daily for moribund or dead animals (once daily on weekends and holidays). Moribund animals were necropsied. Detailed clinical observations were performed once prior to test substance administration and weekly thereafter. Food consumption of the F0 animals (both sexes) was determined during premating and in dams during gestation and lactation periods. In general, body weights of F0 animals were determined once a week. However, during gestation and lactation, F0 females were weighed on days 0, 7, 14, and 20 p.c., on the parturition day, and day 4 post partum. Details of motor activity measurements and functional observational battery assessments on the F0 animals are described in Section 5.4.

Males were exposed for a total of 35 days, followed by necropsy. Females were allowed to litter and rear their pups until 4 days after parturition. Females were exposed for a total of 44 days, followed by necropsy.

MATING

Males and females were mated at a 1:1 ratio for a maximum period of 2 weeks. Females were placed in the cage of the male partner overnight and then vaginal smears were performed to check for the presence of sperm. If detected, that experimental day was noted as "day 0" and the following day "day 1" post-coitum (p.c.). The mating pairs were separated upon sperm detection.

DETERMINATION OF IMPLANTATION SITES

After sacrifice the uterus and ovaries were removed and examined for implantation sites, allowing for calculation of post-implantation loss.

REPRODUCTION DATA

The pairing partners, the number of mating days until the detection of vaginal sperm, and the gestational status of the female were noted for F0 mating pairs. Mating and fertility indices were calculated for males. For females, mating, fertility, gestation and live birth indices were calculated as well post-implantation loss percentage.

Result : Results for food consumption, body weight, clinical and functional observations, motor activity, clinical pathology, gross lesions and pathology for the F0 animals are described in Section 5.4. Gross and histopathological examinations of the reproductive organs of substance-treated male and female rats did not reveal any treatment effects.

MALE REPRODUCTION DATA

The male mating index was 100% for all groups and the fertility index was between 90-100% with no clear relationship to dose.

FEMALE REPRODUCTION DATA

The female mating index was 100% for all groups. No relevant differences in the mean duration until detection of sperm were found. One female in each treated group failed to deliver pups or, upon necropsy, reveal in utero implantations, thus the fertility index was 90% for the treated groups and 100% for the control; this variation is within the normal range. One control female had implantations in utero but delivered no pups; thus the gestation index was 90% for the control. The gestation index was 100% for all treated groups. Implantation was not affected by the test substance; neither was intrauterine embryo-/fetolethality since the post-implantation losses were unaffected by treatment. The test substance did not affect the mean number of F1 pups delivered per dam nor the number of stillborn pups. The live birth index was 94-100% in all test groups. The overall conclusion is that the test substance did not adversely affect reproduction and delivery data for the F0 females.

Test condition : Animals were housed individually in stainless steel wire mesh cages (floor area about 800 cm2), with the following exceptions: for the overnight mating, the females were put into the cages of the males; from day 18 p.c. until sacrifice, the pregnant females were housed in Makrolon cages with their litters. Cages were kept in air conditioned rooms at a temperature of 20-24 degrees C and relative humidity 30-70%. The photoperiod was 12 hours light: 12 hours dark. The food was ground Kilba maintenance diet mouse/rat, and tap water was provided for drinking water. Food and water were available ad libitum except during the fasting period and measurement of motor activity.

Test substance : 2,5-dichloroanisole, Batch# 13418, CAS# 1985-58-3. Purity 99.3% as stated on certificate of analysis.

Conclusion : The NOAEL for reproductive performance and fertility was the highest dose tested, 450 mg/k/d.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

26.12.2007 (8)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	F0 parents: males: 35 days; females: 44 days
Frequency of treatm.	:	F0 animals dosed once per day at the same time in the morning
Duration of test	:	males: 35 days; females: 44 days
Doses	:	0 mg/kg/d, 50 mg/kg/d, 150 mg/kg/d, 450 mg/kg/d
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 150 mg/kg bw
NOAEL teratogen.	:	= 450 - mg/kg bw
Result	:	No test substance related signs of developmental toxicity occurred in progeny
Method	:	other: OECD 422, Combined repeated dose with reproduction/developmental toxicity screen
Year	:	2006
GLP	:	yes
Test substance	:	other TS

Method :

Male and female Wistar rats aged 11-12 weeks were used in the study. All animals were free of disease and females non-pregnant at the beginning of the study. The males and females were raised from separate litters to prevent possible sibling mating.

Three experimental test groups, plus a control, were run with 10 animals of each sex in each group. Dosage levels were 50 mg/kg/d (the expected no adverse effect level dose), 150 mg/kg/d, and 450 mg/kg/d. The control group was treated identically to the experimental animals except for dosage of the test substance. The test substance was administered dissolved in 0.5% carboxymethylcellulose solution in double distilled water and Tween 80. Controls received 0.5% carboxymethlycellulose solution in double distilled water and Tween 80. All animals received 10 mL/kg/d of solution.

TEST SUBSTANCE PREPARATION

The test substance was weighed in a calibrated beaker, topped up with 0.5% Carboxycellulose solution in double distilled water and a few drops of Tween 80 and mixed with a magnetic stirrer. These emulsions were prepared at the beginning of the study and every 7-8 days afterward, based on the results of a stability study which indicated the test emulsions were stable at room temperature for up to 10 days. Analytical monitoring of the test substance preparations was performed at the beginning of the study.

EXPERIMENTAL PROCEDURE AND TIME SCHEDULE

Following acclimation of about 6 days, 80 animals were selected for use. The mean weight of the 40 male animals was 301.4 g (282.3-321.9) and for the 40 female animals 206.8 g (189.4-220.5). Animals were randomly assigned to test groups in a manner that resulted in similar body mass values in each experimental group.

Dosing was conducted once daily via gavage at approximately the same time each day. This was carried out until 1 day prior to sacrifice. After experimental day 13, males and females from the same dose group were placed in mating cages at a 1:1 ratio.

Males and females were mated at a 1:1 ratio for a maximum period of 2 weeks. Females were placed in the cage of the male partner overnight and then vaginal smears were performed to check for the presence of sperm. If detected, that experimental day was noted as "day 0" and the following day "day 1" post-coitum (p.c.). The mating pairs were separated upon sperm

detection.

Checks were made twice daily for moribund or dead animals (once daily on weekends and holidays). Moribund animals were necropsied. Detailed clinical observations were performed once prior to test substance administration and weekly thereafter. Food consumption of the F0 animals (both sexes) was determined during premating and in dams during gestation and lactation periods. In general, body weights of F0 animals were determined once a week. However, during gestation and lactation, F0 females were weighed on days 0, 7, 14, and 20 p.c., on the parturition day, and day 4 post partum.

Males were exposed for a total of 35 days, followed by necropsy. Females were allowed to litter and rear their pups until 4 days after parturition. Females were exposed for a total of 44 days followed by necropsy.

The pups were sexed on the day of birth and weighed one day after birth. Thereafter, the body weight of pups was determined on day 4 post partum. Pups were examined daily for clinical symptoms. All pups were sacrificed on day 4 post partum and examined macroscopically for external and visceral findings at necropsy.

Details of motor activity measurements and functional observational battery assessments on the F0 animals are described in Section 5.4.

Result : Results for food consumption, body weight, clinical and functional observations, motor activity, clinical pathology, gross lesions and pathology for the F0 animals are described in Section 5.4.

The test substance did not affect the mean number of F1 pups delivered per dam nor the number of stillborn pups. The live birth index was 94-100% in all test groups. The number of cannibilized pups, however, was statistically significantly increased in one high dose dam (8 out of 15 liveborn pups); this was considered spontaneous in nature and of no relation to the test substance. The viability index was also affected by this instance of cannibalization ; however, the viability index varied between 98% and 100% in all other test and control groups. Excluding the single affected litter, the viability of the high dose group was 98%. Excluding this single litter, pup body weight and number of runts was not significantly different in the high dose group from the other treatment groups and the control.

The sex ratio of the live F1 pups on the day of birth and at 4 days post partum was unaffected by the test substance. The F1 pups did not show any clinical signs up to sacrifice. Necropsy indicated scattered findings of post mortem autolysis, empty stomach, and absent unilateral testis. These findings occurred without a clear relation to dosing and/or can be found in the historical control data at comparable or even higher incidences.

Test condition : Animals were housed individually in stainless steel wire mesh cages (floor area about 800 cm2), with the following exceptions: for the overnight mating, the females were put into the cages of the males; from day 18 p.c. until sacrifice, the pregnant females were housed in Makrolon cages with their litters. Cages were kept in air conditioned rooms at a temperature of 20-24 degrees C and relative humidity 30-70%. The photoperiod was 12 hours light: 12 hours dark. The food was ground Kilba maintenance diet mouse/rat, and tap water was provided for drinking water. Food and water were available ad libitum except during the fasting period and measurement of motor activity.

Test substance : 2,5-dichloroanisole, Batch# 13418, CAS# 1985-58-3. Purity 99.3% as stated on certificate of analysis.

Conclusion : No test substance related signs of developmental toxicity were seen in the progeny of the F0 parents up to and including the highest dose, 450 mg/kg bw/d. The number of delivered F1 pups/litter, their postnatal survival and

their body weight data remained unaffected by the test substance. Clinical and/or gross necropsy examinations of the F1 pups revealed only findings which were considered to be spontaneous in nature and not related to dose. The NOAEL for developmental toxicity in the progeny is 450 mg/kg bw/d.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
26.12.2007 (8)

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